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Therapeutic Class Review
Combination Products for Helicobacter Pylori

Overview/Summary

Proton-pump inhibitors (PPIs) are a class of antisecretory compounds that suppress gastric acid secretion and are generally recognized as the most potent acid suppressants available.[1-3] Parietal cells line the gastric mucosa and secrete acid into the gastric lumen in response to several stimuli. Within the parietal cell, a gastric transport enzyme known as hydrogen/potassium adenosine triphosphatase (H^+K^+-exchanging ATPase) is involved in the final step in acid secretion. This enzyme, commonly referred to as the proton pump, exchanges potassium ions (K+) for hydrogen ions (H+) resulting in a lower gastric pH. PPIs exert their effect by covalently binding to the proton pump and irreversibly inhibiting this ion exchange, causing an increase in gastric pH.

Helicobacter pylori (*H pylori*), a gram-negative spiral bacteria, has been found to cause gastric and duodenal ulcers and has been linked to the development of gastric cancers.[4] National and international consensus guidelines recommend triple therapy with a PPI, clarithromycin and amoxicillin or metronidazole as a treatment of choice for the eradication of *H pylori*.[5,6] Another first-line option is quadruple therapy with a PPI or histamine H_2-receptor antagonist, bismuth, metronidazole and tetracycline.

There are 3 combination products in this class and all 3 are Food and Drug Administration (FDA) approved for the eradication of *H pylori* in patients with duodenal ulcer disesae.[7-12] Eradication of *H pylori* reduces the risk of duodenal ulcer recurrence. Prevpac® is an administration pack that contains a one-day supply of lansoprazole capsules, amoxicillin capsules and clarithromycin tablets. Helidac® is a blister card that contains a one-day supply of bismuth tablets, metronidazole tablets and tetracycline capsules. Pylera® is a capsule that contains bismuth, metronidazole and tetracycline. Helidac® and Pylera® are approved for administration with a histamine H_2-receptor antagonist and PPI, respectively. While lansoprazole is not available generically, 2 other PPIs (omeprazole and pantoprazole) are available in generic formulations and omeprazole may be obtained over-the-counter. Amoxicillin, clarithromycin, metronidazole, tetracycline and bismuth subsalicylate are available generically.

Clinical trials have demonstrated that these products are effective for their FDA-approved indications. At this time, there are no studies that have demonstrated that use of these combination products are safer, more efficacious or improve clinical outcomes when compared to administration of the individual components as separate prescriptions.

Medications

Table 1. Medications Included Within Class Review[7-12]

Generic Name (Trade Name)	Medication Class	Generic Availability
Amoxicillin*, clarithromycin* and lansoprazole (Prevpac®)	Proton-pump inhibitors	-
Bismuth subcitrate potassium, metronidazole* and tetracycline* (Pylera®)	Anti-infective agents (*Helicobacter pylori*)	-
Bismuth subsalicylate*, metronidazole* and tetracycline* (Helidac®)	Anti-infective agents (*Helicobacter pylori*)	-

*Generic is available in at least one dosage form or strength for this component of the combination product.

Indications

Table 2. Food and Drug Administration-Approved Indications[7-12]

Generic Name	Indication
Amoxicillin, clarithromycin and lansoprazole	Treatment of patients with *H pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate *H pylori*
Bismuth subcitrate potassium, metronidazole and tetracycline	Combination therapy with omeprazole for the treatment of patients with *H pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H pylori*
Bismuth subsalicylate, metronidazole and tetracycline	Combination therapy with a histamine H_2-receptor antagonist for the treatment of patients with *H pylori* infection and duodenal ulcer disease (active or history of duodenal ulcer) to eradicate *H pylori*

Pharmacokinetics

Pharmacokinetic studies have not been performed on coadministration of all three components of Prevpac® or Helidac®.[10,11] Studies have shown no clinically significant interactions of lansoprazole and amoxicillin or lansoprazole and clarithromycin. Upon oral administration, bismuth subsalicylate is almost completely hydrolyzed in the gastrointestinal tract to bismuth and salicylic acid. The pharmacokinetic parameters of Pylera® were similar to those for the individual drugs when administered as separate capsule formulations.[12]

Table 3. Pharmacokinetics[9-13]

Generic Name	Bioavail-ability (%)	Time to Peak Concentration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Amoxicillin	89	1-2	50-70	None	1-2
Bismuth subcitrate potassium	<1 (bismuth)	0.6-3.5 (bismuth)	2.6 per day (bismuth)	Not reported (bismuth)	5-11 days (bismuth)
Bismuth subsalicylate	<1 (bismuth), 80 (salicylic acid)	Not reported (bismuth), 1.8-5 (salicylic acid)	<1 (bismuth), 95 (salicylic acid)	Yes (salicylic acid)	5-11 days intermediate and 21-72 days terminal (bismuth), 2-5 hours (salicylic acid)
Clarithromycin	50	2-4	20-40	Yes (14-OH clarithromycin)	3-7
Lansoprazole	>80	1.7	14-25	Yes (cyclic sulfenamide and disulfide metabolites)	0.9-1.5
Metronidazole	100	1-2	60-80	Yes (2-hydroxymethyl nitroimidazole)	8
Tetracycline	60-90	3.3-4	60	None	8-10

Clinical Trials[14-33]

Clinical trials comparing triple therapy with lansoprazole, amoxicillin and clarithromycin to dual therapy (lansoprazole with amoxicillin or clarithromycin), lansoprazole monotherapy or placebo found that triple therapy provided significantly greater eradication rates of *H pylori* (82%-95% vs 38%-77%, 2%, and 6%,

respectively).[14-16,18] In addition, recurrence of ulcers at six months was lower with triple therapy (7%) compared to dual therapy (13%-23%) and monotherapy (69%).[15] In the clinical trials it was not reported or unclear whether the medications were prescribed as daily administration packs (eg, Prevpac®) or individual prescriptions. In a letter to the editor, Nagahara et al compared the efficacy of administration of lansoprazole 30 mg, amoxicillin 750 mg and clarithromycin 400 mg twice daily for 7 days utilizing a daily dose card (Lansap800®, a product not commercially available in the United States) versus individual tablets.[17] There was no significant difference in eradication rates for *H pylori*, compliance or adverse events between these two groups. (Note: Prevpac® is Food and Drug Administration approved for a 10- or 14-day treatment course and contains different strengths of amoxicillin and clarithromycin.) Meta-analyses and pooled data comparing esomeprazole-, omeprazole-, pantoprazole- and rabeprazole-based regimens to lansoprazole-based therapies have shown similar rates for the eradication of *H pylori* when paired with comparable antibiotic regimens.[18-21]

Head-to-head trials and meta-analyses have reported that bismuth-based quadruple therapy was at least as effective as standard triple therapy for the eradication of *H pylori* and a few studies reported higher eradication rates with quadruple therapy.[5,22,23,26-28,31] Bismuth-based quadruple therapy was also reported to be effective in patients who had received or failed previous *H pylori* treatment regimens.[23-25]

The primary concerns with bismuth-based regimens are the large number of pills, complexity of the dosing schedule and the duration of therapy.[34,35] In effort to improve adherence, blister cards (Helidac®) and triple antibiotic capsules (Pylera®) have been developed. Laine et al reported that a 10-day course of omeprazole plus a triple antibiotic capsule (bismuth, metronidazole and tetracycline) was at least as efficacious as standard therapy with omeprazole, amoxicillin and clarithromycin in the eradication of *H pylori*.[26] The bismuth-based regimen demonstrated effectiveness even in the presence of metronidazole- and clarithromycin-resistant strains of *H pylori* (eradication rates of 80% and 77% in the intention-to-treat analysis, respectively). There are no studies that have compared the safety or efficacy of Helidac® to Pylera®.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Proton-pump Inhibitor-Based Regimens (Triple Therapy)				
Veldhuyzen van Zanten et al[14] Lansoprazole 30 mg, clarithromycin 500 mg, and amoxicillin 1,000 mg BID for 7 days vs placebo	DB, PC, RCT Adult patients with *H pylori* who had functional dyspepsia Patients excluded if they had GERD, history of gastric or esophageal surgery, irritable bowel syndrome, duodenal or gastric ulcers, or a severe comorbidity	N=157 12 months	Primary: Severity of dyspepsia Secondary: *H pylori* eradication rates, proportion of patients requiring additional health care	Primary: Severity of dyspepsia was not significantly different between treatment groups after 12 months (*P*>0.05). Both treatment groups demonstrated improvement of symptoms throughout the study. Secondary: Lansoprazole-clarithromycin-amoxicillin therapy achieved an eradication rate of 82% vs 6% with placebo (*P* value not reported). The proportion of patients requiring additional medication after the 7-day treatment was similar between treatment groups.
Schwartz et al[15] Lansoprazole 30 mg, clarithromycin 500 mg and amoxicillin 1,000 mg BID for 14 days vs lansoprazole 30 mg TID for 14 days vs lansoprazole 30 mg BID, clarithromycin 500 mg BID or TID, for 14 days vs lansoprazole 30 mg BID or TID with amoxicillin	DB, RCT Adult patients with *H pylori* and duodenal ulcers Patients excluded if they had GERD, history of gastric or esophageal surgery, or a severe comorbidity	N=352 4-6 weeks	Primary: *H pylori* eradication rates Secondary: Recurrence of ulcers at 6 months	Primary: The eradication rates with triple therapy (lansoprazole-clarithromycin-amoxicillin; 94%) were significantly greater (*P*<0.05) compared to dual therapy (lansoprazole and clarithromycin or amoxicillin; 53-77%) and lansoprazole monotherapy (2%). Secondary: Recurrence of ulcers at six months was lower with triple therapy (7%) compared to dual therapies (13%-23%) and lansoprazole monotherapy (69%; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
1,000 mg TID for 14 days				
Lamouliatte et al[16] Triple therapy (lansoprazole 30 mg, clarithromycin 500 mg, and amoxicillin 1,000 mg BID) for 14 days vs dual therapy (lansoprazole 30 mg and amoxicillin 1,000 mg BID) for 14 days	PRO, RCT Adult patients with *H pylori* and dyspepsia Patients excluded if they had GERD, history of gastric or esophageal surgery, duodenal or gastric ulcers, or a severe comorbidity	N=50 14 days	Primary: *H pylori* eradication rates Secondary: Not specified	Primary: *H pylori* eradication rates with dual therapy (37.5%) were significantly lower than with triple therapy (95.2%; *P*<0.0002). Secondary: Not specified
Nagahara et al[17] Lansoprazole 30 mg, clarithromycin 400 mg and amoxicillin 750 mg BID for 7 days administered as a daily dose card (Lansap400®*) vs individual tablets	OL, PRO, RCT (letter to the editor) Patients diagnosed with *H pylori* infections accompanying duodenal or gastric ulcers, chronic gastritis or gastric polyp, mean age 52.8 years	N=200 7 days	Primary: *H pylori* eradication measured at least 1 month after completion of therapy Secondary: Not reported	Primary: Cure rates for the groups receiving the daily dose card or the separate tablets were 79.0% (95% CI, 70% to 87%), and 70.0% (95% CI, 60% to 79%), respectively, in the intention-to-treat analysis, and 86.0% (74% to 94%) and 76.1% (95% CI, 64% to 86%), in the per-protocol analysis (no *P* values reported). There was no significant difference in eradication rates between these two groups (*P* values not reported). Compliance did not differ between the two treatment groups (comparative data not reported). Adverse events were reported in 25.5% of patients receiving the daily dose card and 26.6% of patients receiving separate tablets (*P* value not reported). The most frequent adverse events were diarrhea and soft stool. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bazzoli et al[18] Lansoprazole-based *H pylori* therapies vs omeprazole-based *H pylori* therapies	MA Randomized trials investigating the use of lansoprazole-based *H pylori* therapies and other PPI-based *H pylori* therapies utilizing comparable antibiotics regimens and differing only in the PPI utilized	N=1,354 16 trials Treatment duration varied	Primary: *H pylori* eradication rates for lansoprazole therapies Secondary: Comparison of eradication rates for lansoprazole vs omeprazole therapy	Primary: Eradication rates for lansoprazole monotherapy (6-8 week duration) were comparable to dual therapy with lansoprazole (6-8 week duration) and amoxicillin (2-4 week duration; OR, 0.8; 95% CI, 0.3 to 1.9 for gastric ulcers; OR, 1.5; 95% CI, 0.4 to 5.7 for duodenal ulcers). Mean eradication rates for triple therapy with lansoprazole were significantly higher than observed with dual lansoprazole therapy (91.8% vs 57.1%; OR, 8.5; 95% CI, 2.9 to 24.5). Secondary: Mean eradication rates for lansoprazole-based therapies (80.6%) were comparable to omeprazole-based therapies (69.6%; OR, 0.9; 95% CI, 0.6 to 1.3).
Gisbert et al[19] Pantoprazole-based *H pylori* therapies vs lansoprazole- or omeprazole-based *H pylori* therapies	MA Randomized trials investigating the use of pantoprazole-based *H pylori* therapies and lansoprazole- or omeprazole-based *H pylori* therapies utilizing comparable antibiotic regimens and differing only in the PPI utilized	12 trials (Total N not reported) Treatment duration not reported	Primary: *H pylori* eradication rates for pantoprazole therapies Secondary: Comparison of eradication rates for pantoprazole vs other similar (same antibiotics and duration of use) PPI therapies with a focus on similar omeprazole and lansoprazole	Primary: Fourteen-day therapy with pantoprazole 40 mg BID and clarithromycin 500 mg TID therapy resulted in a mean eradication rate of 60%. Mean eradication rates following 7-day therapies were as follows: pantoprazole-amoxicillin-clarithromycin 78%, pantoprazole-clarithromycin-nitroimidazole 84%, and pantoprazole-amoxicillin-nitroimidazole 74%. Secondary: Mean eradication rates for pantoprazole-based therapies (83%) with antibiotics were comparable to other PPI-based therapies (81%; OR, 1.0; 95% CI, 0.61 to 1.64). Mean eradication rates for pantoprazole-based therapies (83%) were comparable to omeprazole-based therapies (82%; OR, 0.91; 95% CI, 0.49 to 1.69). Mean eradication rates for pantoprazole-based therapies (78%)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				were comparable to those with lansoprazole-based therapies (75%; OR, 1.22; 95% CI, 0.68 to 2.17).
Ulmer et al[20] *H pylori* triple therapy with lansoprazole, omeprazole, or pantoprazole for 7 days	MA Clinical trials using PPI-based triple therapy for 7 days in *H pylori* infections	N=8,383 79 trials 7 days	Primary: *H pylori* eradication rates Secondary: Not reported	Primary: Eradication rates for all therapies were 71.9%-83.9% in the intention-to-treat population and 78.5%-91.2% for the per-protocol analysis. Pooled data analysis indicated that lansoprazole-, omeprazole-, or pantoprazole-based therapies are comparable in *H pylori* eradication. Secondary: Not reported
Vergara et al[21] *H pylori* triple therapy with esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole	MA Randomized trials investigating *H pylori* triple therapy with a PPI with comparable antibiotic regimens differing only in the PPI utilized	14 trials 7-14 days	Primary: Direct comparison of eradication rates in the intention-to-treat population between PPIs Secondary: Not reported	Primary: Pooled eradication rates with omeprazole (74.7%) were comparable to rates observed with lansoprazole (76%; OR, 0.91; 95% CI, 0.69 to 1.21). Pooled eradication rates with omeprazole (77.9%) were comparable to rates observed with rabeprazole (81.2%; OR, 0.81; 95% CI, 0.58 to 1.15). Pooled eradication rates with omeprazole (87.7%) were comparable to rates observed with esomeprazole (89%; OR, 0.89; 95% CI, 0.58 to 1.35). Pooled eradication rates with lansoprazole (81%) were comparable to rates observed with rabeprazole (85.7%; OR, 0.77; 95% CI, 0.48 to 1.22). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bismuth-Based Regimens (Quadruple Therapy)				
Uygun et al[22] Lansoprazole 30 mg, amoxicillin 1,000 mg and clarithromycin 500 mg BID for 14 days vs lansoprazole 30 mg BID, bismuth subsalicylate 300 mg QID, metronidazole 500 mg TID and tetracycline 500 mg QID for 14 days	PG, PRO, RCT, SB Patients ≥18 years who were *H pylori* positive with nonulcer dyspepsia Patients excluded for previous treatment for *H pylori;* use of PPIs, histamine H_2-receptor antagonists, NSAIDS, bismuth salts or antibiotics in the previous 4 weeks before enrollment; previous gastric surgery; presence of liver or renal dysfunction, alcohol abuse; known allergy to the prescribed antibiotics; pregnant or lactating	N=240 6 weeks	Primary: Negative ^{14}C-UBT at time of follow-up indicating eradication of *H pylori*, side effects Secondary: Not reported	Primary: Intention-to-treat and per-protocol eradication rates were 70% (95% CI, 61% to 78%; *P*=0.06) and 82.3% (95% CI, 74% to 89%; *P*=0.002) with the bismuth-based quadruple therapy and 57.5% (95% CI, 48% to 66%) and 62.7% (95% CI, 53% to 71%) with lansoprazole-based triple therapy. The overall prevalence of side effects was reported in 18.2% of the patients. Although it was not statistically significant, the number of patients discontinuing therapy for side effects was higher in the bismuth-based regimen than in the lansoprazole-based regimen. Secondary: Not reported
Magaret et al[23] Lansoprazole 30 mg, amoxicillin 1,000 mg and clarithromycin 500 mg BID for 14 days vs lansoprazole 30 mg BID, and bismuth subsalicylate 2 tablets, metronidazole 250 mg and tetracycline 250 mg QID for 14 days	MC, RCT Adult patients failing prior treatment for *H pylori*, documented by a positive ^{14}C-UBT 4 or more weeks following antimicrobial therapy for *H pylori* Patients excluded if they were taking concurrent therapy with antibiotics, PPIs, or histamine H_2-receptor antagonists, or were pregnant.	N=48 6 weeks	Primary: Negative ^{14}C-UBT at time of follow-up indicating cure of infection Secondary: Side effects, compliance	Primary: Per-protocol eradication rates for patients on triple therapy and quadruple therapy were 82% and 80%, respectively (*P*=0.85). Intention-to-treat eradication rates for triple and quadruple therapy were 72% and 65%, respectively (*P*=0.63). Therefore, there were no statistically significant differences between triple therapy and quadruple therapy. Secondary: Compliance in patients receiving triple and quadruple therapy was 89% (*P*=0.98). Side effects were reported in 84% of patients on triple therapy and 82% of patients on quadruple therapy (*P*=0.85). Side effects included nausea (33%), upset stomach (25%), diarrhea (36%), abdominal pain (16%), lightheadedness/dizziness (4%) and fatigue (8%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Uygun et al[24] Lansoprazole 30 mg BID, bismuth subcitrate 300 mg QID, metronidazole 500 mg BID and amoxicillin 1 g BID for 14 days (LBMA) vs lansoprazole, bismuth subcitrate, tetracycline 500 mg QID and amoxicillin for 14 days (LBTA) vs lansoprazole, bismuth subcitrate, metronidazole and tetracycline for 14 days (LBMT)	PRO, RCT Patients with nonulcer dyspepsia and *H pylori* infection who had previously been given lansoprazole, amoxicillin and clarithromycin for 14 days Patients excluded if active peptic ulcer, previous gastric surgery and malignancy, or allergy to study drug	N=278 14 days	Primary: *H pylori* eradication rates measured 60 days after treatment Secondary: Not reported	Primary: Eradication rates were similar among the 3 treatment groups: 74.7% for LBMA, 81.5% for LBTA and 82.1% for LBMT (*P*>0.05). There was no significant difference between the groups when side effects were compared. Bismuth-stained black stools were the most commonly reported side effect by the patients. Secondary: Not reported
Miehlke et al[25] Omeprazole 40 mg QID and amoxicillin 750 mg QID for 14 days vs omeprazole 20 mg BID, bismuth citrate 107 mg QID, metronidazole 500 mg QID and tetracycline	PRO, RCT, XO Patients 18 to 80 years old with at least one previous failure *of H pylori* therapy documented by confirmatory examinations and antimicrobial resistance to both metronidazole and clarithromycin Patients excluded if they had	N=84 26 months	Primary: Two negative biopsy-based tests, histology and rapid urease test, or a validated ^{13}C-UBT to confirm successful treatment Secondary:	Primary: In the per-protocol analysis, patients on high-dose dual therapy and quadruple therapy achieved *H pylori* cure rates of 83.8% and 92.1%, respectively (*P*=0.71). Cure rates using intention-to-treat analysis were 75.6% and 81.4% for high-dose dual therapy and quadruple therapy, respectively, and were not significantly different (*P*=0.60) Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
500 mg QID for 14 days	complicated peptic ulcers, regularly used NSAIDS, and/or antibiotics or bismuth compounds within 4 weeks prior to randomization		Not reported	
Laine et al[26] Omeprazole 20 mg, amoxicillin 1,000 mg and clarithromycin 500 mg BID for 10 days vs omeprazole 20 mg BID plus 3 Helizide®† capsules each containing bismuth biskalcitrate 140 mg, metronidazole 125 mg and tetracycline 125 mg QID for 10 days	AC, MC, RCT Patients with *H pylori* infection and an active duodenal ulcer or history of duodenal ulcer within the past 5 years Patients excluded for upper GI bleeding within the past month; prior attempt to treat *H pylori*; use of antibiotics or bismuth in the past 30 days; regular use of a PPI in the 15 days or of an histamine H_2-receptor antagonist, sucralfate or misoprostol in the 7 days before baseline; chronic use of NSAIDS (except aspirin ≤325 mg daily); contraindication to study drugs; pregnant or lactating; other serious medical conditions or clinically significant laboratory abnormalities at baseline	N=275 10 days	Primary: Eradication of *H pylori* (measured by ^{13}C-UBT at least 29 and 57 days after the end of treatment) Secondary: Effect of resistance to antibiotics on eradication rates, safety, compliance	Primary: Intention-to-treat eradication rates were 87.7% for quadruple therapy and 83.2% for triple therapy (95% CI, –3.9 to 12.8%; *P*=0.29). Secondary: Quadruple therapy eradicated 91.7% metronidazole-sensitive (*P*=0.18 compared to triple therapy) and 80.4% metronidazole-resistant strains (*P*=0.90 compared to triple therapy) in the intention-to-treat analysis. Quadruple therapy eradicated 88.3% clarithromycin-sensitive (*P*=0.36 compared to triple therapy) and 76.9% clarithromycin-resistant strains (*P*=0.004 compared to triple therapy). Triple therapy eradicated 92.1% clarithromycin-sensitive and 21.4% clarithromycin-resistant strains. Triple therapy eradicated 84.5% metronidazole-sensitive and 81.8% metronidazole-resistant strains. Adverse events occurred in 58.5% of patients on quadruple therapy and 59.0% of patients on triple therapy. The most common adverse events were related to the gastrointestinal tract. Compliance was comparable between the 2 study groups with 91% and 94% of patients taking at least 75% of their study medications on quadruple and triple therapy, respectively.
O'Morain et al[27] Omeprazole 20 mg BID plus 3 Helizide®†	MC, OL Patients 18-75 years with duodenal or gastric ulcer or	N=170 10 days	Primary: *H pylori* eradication rates in metronida-	Primary: Overall eradication rates were 93% by intention-to-treat analysis and 97% by per-protocol analysis.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
capsules each containing bismuth biskalcitrate 140 mg, metronidazole 125 mg and tetracycline 125 mg QID for 10 days	nonulcer dyspepsia with confirmed *H pylori* infection		zole-sensitive and resistant strains (determined by ^{13}C-UBT at least 4 and 8 weeks after treatment), adverse events Secondary: Not reported	Eradication rates were 93% and 95% for strains resistant to metronidazole and 95% and 99% for strains sensitive to metronidazole by intention-to-treat analysis and per-protocol analysis, respectively. Mild-to-moderate adverse events were reported in 67% of patients and severe adverse reactions were noted in 7% of patients. The most common types (occurrence >10%) of adverse events in order of occurrence were: stool abnormality, taste perversion, diarrhea, nausea, headache and abdominal pain. Secondary: Not reported
Katelaris et al[28] Pantoprazole 40 mg, amoxicillin 1,000 mg and clarithromycin 500 mg BID (PAC7) vs pantoprazole 40 mg BID, bismuth subcitrate 108 mg QID, tetracycline 500 mg QID, metronidazole 200 mg TID and 400 mg PM for 7 days (PBTM7) vs bismuth subcitrate 108 mg QID, tetracycline 500 mg QID, and metronidazole 200 mg	MC, OL, PG, RCT Adult patients with *H pylori* infection confirmed by a positive urease test and confirmatory histology and ^{13}C-UBT Patients excluded if they received any prior attempt at *H pylori* eradication or concomitant or recent use of PPIs, antibiotics, bismuth or NSAIDS	N=405 8 weeks	Primary: At week 8, ^{13}C-UBT to determine the outcome of eradication therapy Secondary: Compliance, adverse event profile	Primary: By intention-to-treat analysis, the eradication rates for the PAC7, PBTM7, and BTM14 treatment groups were 78%, 82% and 69%, respectively. By per-protocol analysis, the corresponding eradication rates were 82%, 88% and 74%, respectively. In both analysis, the eradication rates for PBTM7 and PAC7 were not significantly different (all $P>0.05$), while eradication rates for PBTM7 were significantly higher than BTM14 ($P=0.01$) Secondary: Adverse effects were common in all treatment groups. Adverse effects that interfered with activities of daily living were significantly higher in the BTM14 group ($P<0.01$). The number of patients who discontinued treatment due to adverse effects was also higher in the BTM14 group (9%) versus the PBTM7 group (3%) and the PAC7 group (2%; *P* values not reported). Noncompliance, defined as less than 90% of study drug taken, was higher with BTM14 than PBTM7 and PAC7 (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
TID and 400 mg PM for 14 days (BTM14)				
Laine et al[29] Ranitidine bismuth citrate* 400 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID vs ranitidine bismuth citrate* 400 mg BID, metronidazole 500 mg TID and tetracycline 500 mg TID	PRO, RCT Adult patients with previously untreated *H pylori* infection documented by ^{13}C-UBT and endoscopic biopsy or rapid quantitative serologic test Patients excluded if they were using antibiotics, PPIs, or bismuth-containing drugs	N=100 6 weeks	Primary: Eradication rates based on ^{13}C-UBT at end of study Secondary: Compliance measured at end of study	Primary: Intention-to-treat analysis showed eradication rates for ranitidine bismuth citrate, amoxicillin, and clarithromycin therapy and ranitidine bismuth citrate, metronidazole and tetracycline therapy were 92% and 80%, respectively (per-protocol analysis showed eradication rates of 96% and 88%, respectively; *P* values were not reported). Secondary: Three patients in the ranitidine bismuth citrate, amoxicillin, and clarithromycin group were not compliant due to side effects of the treatment. Six patients taking ranitidine bismuth citrate, metronidazole and tetracycline therapy were not compliant due to side effects of the treatment; *P* values were not reported.
de Boer et al[30] Ranitidine bismuth citrate* 400 mg BID, tetracycline 500 mg QID and metronidazole 500 mg TID for 7 days vs ranitidine bismuth citrate* 400 mg BID, amoxicillin 1,000 mg BID and clarithromycin 500 mg BID for 7 days vs	OL, PG, RCT Patients with upper gastrointestinal symptoms referred for endoscopic examination and infected with *H pylori* (prestudy endoscopy and end of study endoscopy; CLOtest done at end of study) Patients excluded if they had taken PPIs, bismuth compounds, or antibiotics in the previous 30 days; if they needed drugs that might interact with the study drugs; or if they had	N=168 8 weeks	Primary: Endoscopy performed 6 weeks after completion of treatment to determine *H pylori* infection, defined as a positive CLOtest, confirmed by histology or culture Secondary: Safety	Primary: Logistical regression analysis determined that there was no difference between the 7-day and 14-day treatments. Intention-to-treat analysis cure rate for the ranitidine bismuth citrate, tetracycline and metronidazole treatment group was 86%. The cure rate for the ranitidine bismuth citrate, amoxicillin and clarithromycin treatment group was 92%. The cure rate for the ranitidine bismuth citrate and clarithromycin treatment group was 95%. Per-protocol cure rates were 89%, 93% and 96%, respectively. There was no statistical difference between the three groups (*P* value not reported). Secondary: Side effects were comparable among the treatment groups. Overall, 32% of patients in the ranitidine bismuth citrate, tetracycline and metronidazole treatment group; 18% of the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group; and 23% of the ranitidine bismuth citrate and clarithromycin

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ranitidine bismuth citrate* 400 mg BID, and clarithromycin 500 mg BID for 14 days	contraindications to taking the study medications			treatment group reported side effects during the trial period (*P*=0.249).
Kearney et al[31] Bismuth subsalicylate two tablets QID, metronidazole 250 mg QID, tetracycline 500 mg QID and cimetidine 400 mg BID or famotidine 20 mg BID for 14 days (BMT-H_2) vs bismuth subsalicylate two tablets QID, metronidazole 250 mg QID, tetracycline 500 mg QID and lansoprazole 30 mg BID for 7 days (BMT-PPI) vs metronidazole 500 mg BID, lansoprazole 30 mg BID and clarithromycin 250 mg BID for 7 days (MLC)	OL Patients diagnosed with peptic ulcer disease or prescribed histamine H_2-receptor antagonists or PPIs, and who tested positive with histology, rapid urease or urea breath testing for *H pylori* infection Patients excluded if previously treated for *H pylori*	N=224 6 weeks	Primary: Cure rates for *H pylori* infection at end of study Secondary: Side effects	Primary: The intent-to-treat cure rates for BMT-H_2, BMT-PPI, and MLC were 81%, 87% and 90%, respectively. The corresponding per-protocol cure rates were 84%, 91% and 92%. Comparison of the cure rates between each treatment groups found no significant differences (all *P*>0.05). Secondary: The side-effect profile for the 3 treatment groups revealed no significant differences in the frequency of the most common side effects, diarrhea and constipation (*P* value not reported). Metallic taste was significantly more severe in the MLC group (*P*=0.04). Nausea was significantly more common in the MLC group than the BMT-H_2 group (*P*=0.04). There were no significant differences in the frequency of dizziness/lightheadedness, cramping, or other side effects between the BMT-H_2 and MLC groups, and between BMT-PPI and BMT-H_2 groups. Severe headaches were significantly more frequent in the BMT-PPI group than the BMT-H_2 group (*P*=0.02). A significantly higher number of patients discontinued therapy due to adverse events in the BMT-H_2 and BMT-PPI treatment groups than the MLC group (*P*=0.049).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Saad et al[32] Levofloxacin-based *H pylori* triple therapies vs bismuth-based *H pylori* quadruple therapies	MA, RCT Randomized trials comparing the use of 10-day levofloxacin-based triple therapy to 7-day bismuth-based quadruple therapy	N=854 11 trials 8 weeks	Primary: Eradication rates, incidence of adverse events, incidence of discontin-uation due to adverse events Secondary: Eradication rates of 7-day therapy versus 10-day therapy, eradication rates with levofloxacin 250 mg BID versus 500 mg BID	Primary: The results of 4 trials comparing levofloxacin-based triple therapy to bismuth-based quadruple therapy revealed eradication rates of 87% and 60%, respectively (*P* value not reported). Three of the 4 studies reported adverse-event frequency for levofloxacin-based therapy and bismuth-based therapy as 18.1% and 32.5%, respectively (*P* value not reported). Four trials demonstrated that adverse events were less likely to cause discontinuation of therapy with 10-day levofloxacin-based therapy than bismuth-based therapy (*P* value not reported). Secondary: Eleven trials compared the results of 7 days of levofloxacin-based therapy with those of 10 days of therapy. The corresponding eradication rates were 68% and 87%, respectively. Eight trials comparing efficacy of levofloxacin 250 mg BID to 500 mg BID revealed no significant difference in the eradication rates, which were 84% and 81%, respectively (*P* values not reported).
Perri et al[33] Pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 150 mg every other day for 10 days (RIF 150 mg group) vs pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 300 mg every other day for 10 days (RIF 300 mg group)	OL, PRO, RCT Patients with *H pylori* infection confirmed by ^{13}C-UBT after failure of one or more standard regimens Patients excluded if they had received previous treatment with an antibiotic, H_2-receptor antagonist, bismuth, PPI, or NSAID within the last month, or if they previously had quadruple PPI-bismuth-based therapy	N=135 6 weeks	Primary: Eradication rates as defined by negative ^{13}C-UBT 4 weeks after end of treatment Secondary: Side effect rates reported after end of treatment	Primary: By intention-to-treat analysis, eradication rate for the pantoprazole, amoxicillin and rifabutin 150 mg treatment group (RIF 150 mg group) was 66.6%. Eradication rate for pantoprazole, metronidazole, bismuth citrate, and tetracycline (quadruple therapy group) was also 66.6%. The eradication rate for pantoprazole, amoxicillin, and rifabutin 300 mg (RIF 300 mg group) was 86.6%, which was significantly different than the other two treatment groups (*P*<0.025). Secondary: There was a significant difference in the side effects observed in rifabutin-treated patients vs patients receiving quadruple therapy. The rates of side effects were 9%, 11% and 47% (*P*<0.0001), for the triple therapies with the RIF 150 mg group, RIF 300 mg group, and quadruple therapy group, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs pantoprazole 40 mg BID, metronidazole 250 mg TID, bismuth citrate 240 mg BID and tetracycline 500 mg QID for 10 days (quadruple therapy group)				

*Product not commercially available in the United States
†Product contains similar ingredients to Pylera®
Drug regimen abbreviations: BID=twice daily, PM=at night, PPI=proton-pump inhibitor, QID=four times daily, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SB=single blind, XO=crossover
Miscellaneous abbreviations: GERD=gastroesophageal reflux disease, NSAIDS=nonsteroidal anti-inflammatory drugs, UBT=urea breath test

Special Populations

Table 5. Special Populations[9-13]

Generic Name	Population and Precaution					
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk	Other
Amoxicillin	Caution advised for Prevpac® in the elderly. Prevpac® not studied in the pediatric population.	Dosage reduction should be considered.	No dosage adjustment required.	B	Yes (1.3%-5.0%)	None.
Bismuth subcitrate potassium	No dosage adjustment required in the elderly. Pylera® not studied in the pediatric population.	Dosage reduction should be considered.	No dosage adjustment required.	Not rated.	Unknown.	None.
Bismuth subsalicylate	No dosage adjustment required in the elderly. Helidac® not studied in the pediatric population.	Dosage reduction should be considered.	No dosage adjustment required.	Not rated.	Unknown.	Children and teenagers recovering from chicken pox or the flu should not use bismuth subsalicylate to treat nausea or vomiting; they should be advised to consult a doctor to rule out Reye's syndrome.
Clarithromycin	Caution advised for Prevpac® in the elderly.	Dosage reduction should be considered.	No dosage adjustment required.	C	Unknown.	None.

Generic Name	Population and Precaution					
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk	Other
	Prevpac® not studied in the pediatric population.					
Lansoprazole	Caution advised for Prevpac® in the elderly. Prevpac® not studied in the pediatric population.	No dosage adjustment required.	Dosage adjustment for patients with severe liver disease should be considered.	B	Unknown.	Oral disintegrating tablets contain phenylalanine.
Metronidazole	No dosage adjustment required in the elderly. Helidac® and Pylera® not studied in the pediatric population.	Dosage reduction should be considered in renal failure.	Dosage reduction should be considered for severe hepatic disease.	B	Yes (100%)	Caution in patients with central nervous system diseases and/or history of blood dyscrasias.
Tetracycline	No dosage adjustment required in the elderly. Helidac® and Pylera® not studied in the pediatric population.	Dosage reduction should be considered.	No dosage adjustment required.	D	Yes (58%-128%)	

Adverse Drug Events

The most frequently reported adverse events for the bismuth-based therapies involve the gastrointestinal tract.[10,12] The most common adverse reactions reported with Prevpac® (amoxicillin, clarithromycin and lansoprazole) when given concomitantly for 14 days were diarrhea, headache and taste perversion.[11] Symptomatic response to therapy with Prevpac® does not preclude the presence of gastric malignancy.

Bismuth containing products may cause a temporary and harmless darkening of the tongue and/or black stool, which should not be confused with melena.[10,12] There have been rare reports of neurotoxicity associated with excessive doses of various bismuth-containing products. Seizures and peripheral

neuropathy have been reported in patients treated with metronidazole and are most prevalent in patients taking high doses for prolonged treatment periods.

The antianabolic action of tetracycline may cause an increase in blood urea nitrogen.[10,12] In patients with significantly impaired renal function, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia, and acidosis. Rare instances of esophagitis and esophageal ulceration have been reported in patients taking tetracycline, which can be minimized by taking tetracycline products with adequate amounts of fluid, particularly with the bedtime dose.

Table 6. Adverse Drug Events (%)[9-12]

Adverse Event(s)	Amoxicillin, Clarithromycin and Lansoprazole	Bismuth Subcitrate Potassium, Metronidazole and Tetracycline*	Bismuth Subsalicylate, Metronidazole and Tetracycline
Central Nervous System			
Anxiety	-	1.4	-
Asthenia	-	4.1	-
Confusion	<3	-	-
Dizziness	<3	3.4	1.5
Headache	6.0	8.2	1.5
Insomnia	-	-	1.1
Neurotoxicity	-	✔	✔
Paresthesia	-	✔	1.1
Pseudotumor cerebri	-	✔	✔
Seizure	-	✔	✔
Dermatological			
Photosensitivity reaction	-	✔	✔
Rash	-	2.1	-
Skin reactions	<3	-	-
Gastrointestinal			
Abdominal pain	<3	8.8-13	6.8
Anal discomfort	-	-	1.1
Anorexia	-	-	1.5
Black stools	-	✔	-
Constipation	-	-	1.9
Dark stools	<3	✔	✔
Diarrhea	7.0	8.8-13	6.8
Discoloration of teeth	-	✔	✔
Discoloration of tongue	<3	✔	1.5
Dry mouth	<3	1.4	-
Duodenal ulcer	-	-	1.1
Dyspepsia	-	8.8-13	1.5
Esophagitis/esophageal ulceration	-	✔	✔
Flatulence	-	-	1.1
Gastritis	-	1.4	-
Gastroenteritis	-	1.4	-
Gastrointestinal hemorrhage	-	-	1.1
Glossitis	<3	-	-
Melena	-	-	3.0
Nausea	<3	8.2-12	12.0
Oral moniliasis	<3	-	-
Rectal itching	<3	-	-

Adverse Event(s)	Amoxicillin, Clarithromycin and Lansoprazole	Bismuth Subcitrate Potassium, Metronidazole and Tetracycline*	Bismuth Subsalicylate, Metronidazole and Tetracycline
Stomatitis	<3	-	-
Stool abnormality	-	15.6	1.1
Taste perversion	5.0	4.8	1.1
Vomiting	<3	1.4	1.5
Hematologic			
Leukopenia	-	✔	-
Laboratory Test Abnormalities			
Elevate BUN	-	✔	✔
Elevated SGOT	-	1.4	-
Elevated SGPT	-	2.0	-
Lab test abnormality	-	2.7	-
Respiratory			
Pharyngitis	-	2.0	-
Respiratory disorders	<3	-	-
Rhinitis	-	1.4	-
Sinusitis	-	-	1.1
Upper respiratory infection	-	-	2.3
Other			
Anaphylaxis	✔	-	-
Flu syndrome	-	5.4	-
Infection	-	1.4-2.0	-
Myalgia	<3	-	-
Pain, chest	-	1.4	-
Pain, general/back	-	2.0	1.1
Palpitation	-	1.4	-
Urinary abnormality	-	2.0	-
Vaginitis	<3	4.1	-

BUN=blood nitrogen urea, SGOT=serum glutamic-oxaloacetic transaminase, SGPT= serum glutamic-pyruvic transaminase
*Plus omeprazole
✔ Percent not specified.
- Event not reported or incidence <1%.

Contraindications / Precautions

Helidac® and Pylera® are contraindicated in pregnant or nursing women; pediatric patients; patients with renal or hepatic impairment; and in those with known hypersensitivity to bismuth subcitrate potassium or bismuth subsalicylate, metronidazole or other nitroimidazole derivatives or tetracyclines.[10,12] Helidac® is also contraindicated in patients who have a known allergy to aspirin or salicylates.[10] If taken with aspirin and ringing in the ears occurs, the prescriber should be consulted concerning discontinuation of the aspirin therapy until Helidac® therapy is completed. Metronidazole has been shown to be carcinogenic in animals and carries a black box warning regarding this risk. (See Table 7.)

Prevpac® is contraindicated in patients with known hypersensitivity to Prevacid®, any macrolide antibiotic or any penicillin.[11] Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Before initiating therapy with amoxicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. Concomitant administration of Prevpac® with any of the following drugs is contraindicated: cisapride, pimozide, astemizole, terfenadine, ergotamine or dihydroergotamine. As with other macrolides, clarithromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of these combination products and other antibacterial drugs, Helidac®, Prevpac® and Pylera® should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.[10-12] As with other anti-infective agents, the use of these combination products to eradicate *H pylori* may result in superinfections with mycotic or bacterial pathogens, including *Clostridium difficile.* Treatment regimens may need to be modified and appropriate therapy instituted.

Table 7. Black Box Warning for Metronidazole

WARNING
Metronidazole has been shown to be carcinogenic in mice and rats. (See PRECAUTIONS.) Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the INDICATIONS AND USAGE section below.

Drug Interactions

Table 8. Drug Interactions[8-12]

Generic Name	Interacting Medication or Disease	Potential Result
Amoxicillin	Methotrexate	Amoxicillin may reduce renal clearance of methotrexate. Concurrent use may result in methotrexate toxicity.
Amoxicillin	Oral contraceptives	Amoxicillin may decrease the enterohepatic circulation of oral contraceptives, reducing their effectiveness.
Amoxicillin	Probenecid	Coadministration of probenecid and amoxicillin may cause increases in amoxicillin levels due to decreased renal tubular secretion.
Amoxicillin	Warfarin	Amoxicillin may increase the bleeding risk of warfarin through an unknown interaction. International normalized ratio should be monitored closely.
Clarithromycin	Aminophylline, oxtriphylline, theophylline	Clarithromycin may inhibit the metabolism of theophylline. Theophylline may reduce bioavailability and increase renal clearance of oral clarithromycin.
Clarithromycin	Antiarrhythmic agents (amiodarone, bretylium, disopyramide, dofetilide, procainamide, quinidine, sotalol)	An additive or synergistic increase in the QT interval may result. The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
Clarithromcyin	Astemizole	Coadministration is contraindicated due to postmarketing reports of serious cardiac arrhythmias and fatalities. Clarithromycin may inhibit the metabolism of this drug.
Clarithromycin	Atorvastatin, lovastatin, simvastatin	Clarithromycin may inhibit the metabolism of atorvastatin, lovastatin, or simvastatin.
Clarithromycin	Alprazolam, diazepam, midazolam, triazolam	Clarithromycin may decrease the metabolism of certain benzodiazepines.
Clarithromycin	Carbamazepine	Clarithromycin may inhibit carbamazepine metabolism, leading to decreased clearance.
Clarithromycin	Cisapride	Coadministration is contraindicated due to postmarketing reports of serious cardiac arrhythmias and fatalities. Clarithromycin may inhibit the metabolism of this drug.
Clarithromycin	Colchicine	Clarithromycin may inhibit the metabolism of colchicine.

Generic Name	Interacting Medication or Disease	Potential Result
		Increased colchicine serum concentrations with toxicity (including death) may occur. Avoid this combination.
Clarithromycin	Cyclosporine	Clarithromycin may interfere with cyclosporine metabolism and may increase the rate and extent of absorption or reduce volume of distribution.
Clarithromycin	Digoxin	Clarithromycin may inhibit renal tubular *P* glycoprotein excretion of digoxin.
Clarithromycin	Dihydroergotamine, ergotamine	Clarithromycin may interfere with the hepatic metabolism of ergotamine. Coadministration is contraindicated.
Clarithromycin	Diltiazem	Diltiazem may inhibit the metabolism of clarithromycin.
Clarithromycin	Eplerenone	Clarithromycin may inhibit the metabolism of eplerenone. Elevated eplerenone levels may increase the risk of hyperkalemia and associated serious, sometimes fatal, arrhythmias.
Clarithromycin	Grapefruit Juice	Grapefruit juice may inhibit the metabolism of clarithromycin.
Clarithromycin	Gatifloxacin, levofloxacin, moxifloxacin	Avoid levofloxacin and use gatifloxacin and moxifloxacin with caution in patients receiving macrolide and related antibiotics. The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
Clarithromycin	Pimozide	Coadministration is contraindicated due to postmarketing reports of serious cardiac arrhythmias and fatalities. Clarithromycin may inhibit the metabolism of this drug.
Clarithromycin	Ranolazine	Clarithromycin may inhibit the metabolism of ranolazine. Ranolazine levels may be elevated, increasing the risk of life-threatening cardiac arrhythmias.
Clarithromycin	Rifabutin, rifampin, rifapentine	The metabolism of rifabutin may be inhibited. The metabolism of clarithromycin may be increased with coadministration of rifabutin, rifampin and rifapentine.
Clarithromycin	Tacrolimus	Metabolism of tacrolimus may be inhibited.
Clarithromycin	Terfenadine	Coadministration is contraindicated due to postmarketing reports of serious cardiac arrhythmias and fatalities. Clarithromycin may inhibit the metabolism of this drug.
Clarithromycin	Verapamil	Clarithromycin may inhibit the metabolism of verapamil.
Clarithromycin	Warfarin	Clarithromycin may reduce the total body clearance of warfarin.
Lansoprazole	Azole antifungals	Proton pump inhibitors (PPIs) may reduce the bioavailability of certain azole antifungals, reducing plasma levels and antifungal activity. Concurrent use should be avoided. If concurrent use is necessary, administer the oral azole antifungal with an acidic beverage.
Lansoprazole	Protease inhibitors	PPIs may reduce the dissolution of certain protease inhibitors, reducing gastrointestinal absorption and antiviral activity. Saquinavir plasma levels may increase. Dose adjustment of some protease inhibitors may be required with concurrent administration. The use of PPIs

Generic Name	Interacting Medication or Disease	Potential Result
		with atazanavir is not recommended.
Lansoprazole	Warfarin	Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in International Normalized Ratio and prothrombin time.
Metronidazole	Amprenavir	Amprenavir contains propylene glycol. Propylene glycol is metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway, and patients being treated concurrently with metronidazole may not metabolize and eliminate propylene glycol. Coadministration of amprenavir oral solution and metronidazole is contraindicated.
Metronidazole	Warfarin	The anticoagulant effect of warfarin may be enhanced and hemorrhage could occur due to decreased metabolism of warfarin by metronidazole. Monitor the patient more frequently for signs and symptoms of bleeding. A lower dose of warfarin may be required.
Metronidazole	Barbiturates	Therapeutic failure of metronidazole may result from barbiturate induction of metronidazole metabolism resulting in more rapid elimination and lower serum concentrations. Observe for metronidazole treatment failure, and increase the metronidazole dose accordingly.
Metronidazole	Busulfan	Busulfan trough concentrations may be elevated, increasing risk of serious toxicity. Avoid coadministration of busulfan and metronidazole.
Metronidazole	Ergot derivatives	Metronidazole and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative and serious toxicity. Concomitant use is contraindicated.
Metronidazole	Ethanol	A disulfiram-like reaction may occur with concomitant ingestion. Metronidazole may inhibit aldehyde dehydrogenase, thus causing accumulation of acetaldehyde. Avoid concomitant ethanol ingestion and for at least 1 day afterwards.
Metronidazole	Fluorouracil	Coadministered metronidazole significantly reduces fluorouracil clearance resulting in more severe fluorouracil side effects, without enhanced therapeutic results. Avoid concurrent administration of fluorouracil and metronidazole. If not possible, monitor patients for fluorouracil toxicity.
Salicylates	Angiotensin-converting enzyme (ACE) inhibitors	Inhibition of prostaglandin synthesis may reduce the hypotensive and vasodilator effects of ACE inhibitors. Monitor blood pressure and hemodynamic parameters. The interaction may be minimized by reducing the dose of salicylate to less than 100 mg/day, converting to a nonaspirin antiplatelet agent, or continuing the salicylate and converting from an ACE inhibitor to an angiotensin-receptor blocker.
Salicylates	β-Blockers	Salicylates may inhibit biosynthesis of prostaglandins involved in the antihypertensive activity of β-blockers

Generic Name	Interacting Medication or Disease	Potential Result
		thus attenuating the blood pressure lowering effects. Monitor blood pressure in hypertensive patients. Monitor left ventricular ejection fraction in patients with chronic heart failure. Consider lowering the dose of salicylate.
Salicylates	Insulin	Basal insulin concentrations are increased and the acute insulin response to a glucose load is enhanced. Monitor blood glucose concentrations and tailor insulin regimen as needed.
Salicylates	Methotrexate	Salicylates may decrease methotrexate renal clearance and plasma protein binding and increase the toxic effects of methotrexate. Closely monitor methotrexate plasma levels to guide dose adjustment. Decreased doses of methotrexate or prolonged regimens of leucovorin rescue may be indicated when salicylates are coadministered.
Salicylates	Valproic acid	Salicylates may displace valproic acid from protein binding sites and alter valproic acid's metabolic pathways, which may result in an increased free fraction, possibly leading to toxic effects of valproic acid. Monitor serum valproic acid concentrations, symptoms of valproic acid toxicity, and liver enzymes.
Tetracycline	Digoxin	Coadministration of digoxin and tetracycline may result in increased serum levels of digoxin. Monitor patients for increased digoxin levels and signs of digoxin toxicity. Decreasing the dose of digoxin may be necessary.
Tetracycline	Penicillins	The pharmacologic and therapeutic action of penicillins could be reduced by the bacteriostatic action of tetracyclines. Avoid combination use if at all possible.
Tetracycline	Oral contraceptives	Tetracycline may decrease the enterohepatic circulation of oral contraceptives, reducing their effectiveness.
Tetracycline	Retinoids	Risk of pseudotumor cerebri may be increased due to the additive or synergistic side effect of tetracycline and retinoids. Concomitant use of acitretin or isotretinoin is not recommended.
Tetracycline	Warfarin	Tetracycline may directly affect hemostasis. The action of warfarin may be increased.

Dosing and Administration

Table 9. Dosing and Administration[10-12]

Generic Name	Adult Dose	Pediatric Dose	Availability
Amoxicillin, clarithromycin and lansoprazole	*H pylori* eradication: Amoxicillin 1,000 mg, clarithromycin 500 mg and lansoprazole 30 mg administered together twice daily (morning and evening) for 10 or 14 days Note: take before eating.	Safety and efficacy in children have not been established.	Individual daily administration packs, each pack containing: 4 Amoxicillin capsules: 500 mg 2 Clarithromycin

Generic Name	Adult Dose	Pediatric Dose	Availability
			tablets: 500 mg 2 Lansoprazole capsules: 30 mg
Bismuth subcitrate potassium, metronidazole and tetracycline	*H pylori* eradication: 3 capsules four times daily, after meals and at bedtime, for 10 days (note: 1 omeprazole 20 mg capsule should be taken twice daily with Pylera® after the morning and evening meal for 10 days) Swallow Pylera® capsules whole with a full glass of water (8 ounces).	Safety and efficacy in children have not been established.	Capsules, each capsule containing: Bismuth subcitrate potassium 140 mg Metronidazole 125 mg Tetracycline 125 mg
Bismuth subsalicylate, metronidazole and tetracycline	*H pylori* eradication: Bismuth subsalicylate 524.8 mg, metronidazole 250 mg, and tetracycline 500 mg four times daily at mealtimes and bedtime for 14 days in conjunction with a histamine H_2-receptor antagonist approved for the treatment of acute duodenal ulcer The metronidazole tablets and tetracycline capsules should be swallowed whole with a full glass of water (8 ounces).	Safety and efficacy in children have not been established.	Blister cards, each card containing: 8 Bismuth subsalicylate chewable tablets: 262.4 mg 4 Metronidazole tablets: 250 mg 4 Tetracycline capsules: 500 mg

Other Key Facts

- Both triple and quadruple therapy regimens for *H pylori* eradication are complex and require administration of numerous pills. While the use of combination products may reduce the number of prescriptions that a patient receives, they do not significantly reduce the pill burden.
- There are no studies that have demonstrated that the use of daily administration packs, blister cards or triple antibiotic capsules improves clinical outcomes.

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American College of Gastroenterology: **Guideline on the Management of *Helicobacter pylori* Infection (2007)**[5]	• In the United States (US), the recommended primary therapies for *H pylori* infection include: a proton pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole (clarithromycin-based triple therapy) for 14 days for eradication rates of 70%-85% or a PPI or histamine H_2-receptor antagonist, bismuth, metronidazole, and tetracycline (bismuth-based quadruple therapy) for 10-14 days for eradication rates of 75%-90%.

Clinical Guideline	Recommendation(s)
	• The currently available PPIs perform comparably when used in the triple therapy regimens. A meta-analysis of 13 studies suggests that twice daily dosing of a PPI (lansoprazole, omeprazole, pantoprazole and rabeprazole) in clarithromycin-based triple regimens is more effective than once daily dosing. • Sequential therapy consisting of a PPI and amoxicillin for 5 days followed by a PPI, clarithromycin, and tinidazole for an additional 5 days may provide an alternative to clarithromycin-based triple or bismuth-based quadruple therapy but requires validation within the US before it can be recommended as a first-line therapy. • In patients with persistent *H pylori* infection, every effort should be made to avoid antibiotics that have been previously taken by the patient. Bismuth-based quadruple therapy for 7-14 days is an accepted salvage therapy. Levofloxacin-based triple therapy for 10 days is another option for patients with persistent infection but this regimen requires validation in the US.
European *Helicobacter pylori* Study Group: **Current Concepts in the Management of *H pylori* Infection–The Maastricht III Consensus Report (2007)**[6]	• Recommended first-line treatment is a PPI, clarithromycin and amoxicillin or metronidazole in populations with less than 15%-20% clarithromycin resistance. In populations with less than 40% metronidazole resistance a regimen containing a PPI, clarithromycin and metronidazole is preferable. A 14-day treatment regimen is 12% more effective than a 7-day regimen. A 7-day treatment regimen may be acceptable where local studies show that it is effective. • Bismuth-based quadruple therapies (10 or 14 days) are alternative first-choice treatments. • Bismuth-based quadruple therapies remain the best second-choice treatment. If not available, a PPI, amoxicillin or tetracycline and metronidazole are recommended.

Conclusions

This review encompasses three combination products that are Food and Drug Administration (FDA) approved for the eradication of Helicobacter *pylori*. Prevpac® is an administration pack that contains a one-day supply of lansoprazole capsules, amoxicillin capsules and clarithromycin tablets.[11] Helidac® is a blister card that contains a one-day supply of bismuth tablets, metronidazole tablets and tetracycline capsules.[10] Pylera® is a triple antibiotic capsule that contains bismuth, metronidazole and tetracycline.[12] Helidac® and Pylera® are approved for administration with a histamine H_2-receptor antagonist and PPI, respectively. While lansoprazole is not available generically, 2 other proton pump inhibitors (PPIs) (omeprazole and pantoprazole) are available in generic formulations, and omeprazole may be obtained over-the-counter. Amoxicillin, clarithromycin, metronidazole, tetracycline and bismuth subsalicylate are available generically.

National and international consensus guidelines recommend triple therapy with a PPI, clarithromycin and amoxicillin or metronidazole as a treatment of choice for the eradication of *H pylori*.[5,6] Clinical trials comparing triple lansoprazole-based therapy to dual therapies (lansoprazole with amoxicillin or clarithromycin) and to lansoprazole monotherapy found that triple therapy produced significantly greater eradication rates of *H pylori*. Nagahara et al reported no difference in eradication rates, compliance and adverse events when lansoprazole, amoxicillin and clarithromycin were administered using a daily dose card versus the individual components.[17] Meta-analyses comparing other PPI-based therapies to lansoprazole-based therapy have shown similar eradication rates for *H pylori* when paired with comparable antibiotic regimens. National and international consensus guidelines do not give preference to one PPI over another for the eradication of *H pylori*. The American College of Gastroenterology states that currently available PPIs perform comparably when used in triple therapy regimens.[5]

Quadruple therapy with a PPI or histamine H_2-receptor antagonist and bismuth, metronidazole and tetracycline is also considered a first-line option for the eradication of *H pylori*.[5,6] Bismuth-based quadruple therapy offers eradication rates that are at least as effective as triple therapy.[5,22,23,26-28,31] Bismuth-based quadruple therapy was also reported to be effective in patients who had received or failed previous H pylori treatment regimens.[23-25] Although minor side effects with bismuth-based quadruple therapy occur commonly, the frequency of moderate or severe side effects is not greater than with clarithromycin-based triple therapy. The primary concerns with bismuth-based regimens are the large number of pills, complexity of the dosing schedule and the duration of therapy.[34] In an effort to improve adherence, blister cards (Helidac®) and triple antibiotic capsules (Pylera®) have been developed. There are limited studies evaluating these products, particularly with regards to improving compliance and clinical outcomes. Laine et al reported that a 10-day course of omeprazole plus a triple antibiotic capsule (bismuth, metronidazole and tetracycline) was at least as effective as standard therapy with omeprazole, amoxicillin and clarithromycin in the eradication of *H pylori*.[26] Of note, the bismuth-based regimen demonstrated *H pylori* eradication rates of 77%-92%, even in the presence of metronidazole- and clarithromycin-resistant strains. There are no studies that have compared the safety or efficacy of Helidac® to Pylera®.

While a PPI combined with amoxicillin and clarithromycin is the most commonly prescribed regimen for the eradication of *H pylori* in the Western world, effectiveness of triple therapy is decreasing due to an increase in antibiotic resistance.[34,35] At this time, quadruple therapy containing a PPI, bismuth, metronidazole and tetracycline remains the best second-choice treatment and has shown effectiveness even in the presence of antibiotic resistance.[5,34,35] The use of alternative regimens and therapies, such as other antimicrobial agents and sequential therapy, requires further validation in the United States.[5]

At this time, there are no studies that have demonstrated that use of these combination products are safer, more efficacious or improve clinical outcomes when compared to administration of the individual components as separate prescriptions. Therefore, all brand products within the class reviewed are comparable to each other and offer no significant clinical advantage over other alternatives in general use.

Recommendations

In recognition of the following factors:

- both quadruple therapy (with bismuth, metronidazole, tetracycline and a PPI or histamine H_2-receptor antagonist) and triple therapy (with amoxicillin, clarithromycin and a PPI) are currently well-recognized as first-line treatment options for the eradication of *H pylori*
- all individual components of these triple- and quadruple-therapy regimens are available in generic form
- a lack of clinical trials demonstrating that one combination is safer or more efficacious than another within this class
- a lack of clinical trials demonstrating better clinical outcomes with the prepackaged formulations versus coadministration of the individual components as separate entities

…it is recommended that no changes be made to the current approval criteria.

Currently Prevpac, the only combination product for eradication of H.Pylori managed by OVHA, does not require a prior authorization.

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